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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,960	08/03/2001	Michael W. Leviten	R-441	9830

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/922,960	LEVITEN, MICHAEL W.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08/03/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply filed 10/07/2004 has been received. Claims 1-40 have been cancelled. Claims 41-46 have been added, are pending and under consideration in the instant office action.

Specification

The objection to the specification set forth in the previous office action mailed 07/09/04 is withdrawn in light of Applicant's amendment to the specification. The data in Table 1 is now consistent with that in the specification. However, the amendment necessitates a new grounds of objection.

The amendment filed 10/07/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant has amended the specification at Table 1, page 52 to be consistent with the text at page 52, lines 13-15, which was also amended in the reply dated 06/07/04. The instant amendment adds new matter to the specification in that the specification now teaches a different data set and phenotype for the mice of the invention from that of the specification as originally filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 101/112

Definitions:
[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in

the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

See also the MPEP § 2107 - 2107.02.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-46 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The rejection set forth on pages 2-6 of the previous office action mailed 07/09/2004 is maintained as it applies to newly added claims 41-46 for the reasons of record.

The instant specification has discussed that the mice of the instant invention can be used as models of disease to screen for drug therapies and as a tool for studying the function of a ubiquitin ligase E3 gene. As set forth in the previous office action, these uses fail to meet the standards of a credible, specific, substantial and well-established utility required under 35 U.S.C. 101. In summary, the utilities provided by Applicant for the claimed mouse are not specific or substantial and therefore are not well established because the use of the mouse in screening for drugs to treat an unknown disease is not specific. The use for the claimed mouse in characterizing the function of a ubiquitin ligase E3 gene is not substantial. That SEQ ID NO:1, asserted to encode a ubiquitin ligase E3, is not even a credible assertion because SEQ ID NO:1 is known in the art as an RCC1-like G exchanging factor (refer to page 5, paragraph 2 of the previous office action; see also Merla, 2002) and is not demonstrated to have ubiquitin ligase activity. Therefore the use of a mouse lacking an activity other than ubiquitin ligase E3 to study ubiquitin ligase E3 function is not credible. The basis for this rejection is further set forth in the previous office action and in the guidelines above.

Applicant has argued that the Patent Office guidelines state that a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose (pages 4-7). Applicant cites excerpts from an NIH website and Albert's Molecular Biology of the Cell (pages 4-6 of Applicant's response) in establishing that knockout mice are invaluable tools of scientific research. Applicant also cites the MPEP in discussing the utility of research tools (pages 6 of Applicant's response; MPEP 2107.01, I). In general, Applicant does not understand how the invention cannot have utility when the invention is being used by one of skill in the art and has clearly been accepted as useful by several leaders in the field of transgenic technology.

In response, the instant invention has failed to meet the requirements of possessing a well-established utility and for a use with any particular practical purpose. A well-established utility and a utility with a particular practical purpose is one that is specific and substantial (see MPEP 2107(II)(A)(3)(ii) and MPEP 2107 (II)(B)(1)). The utility of the instant invention is neither specific nor substantial for reasons of record. Applicant is reminded that the utility guidelines (see above) expressly state that utilities requiring further research to identify or reasonably confirm a use do not define substantial utilities. Examples of uses that are not considered substantial utilities include basic research in studying the claimed product and use to screen for therapeutics for an unspecified disease. The use of the invention by the skilled artisan does not impart patentability or patentable use on the invention for reasons set forth above.

With specific respect to Applicant's applied references, the validity of the opinion of the NIH and Albert with respect to the value of the knockout mouse in determining gene function is not questioned. However, the use of a mouse to determine gene function, as set forth above, does

not meet the requirement that a utility be specific and substantial, and therefore, does not fulfill the requirements of utility under 35 USC 101. With respect to MPEP 2107.01, I, a gas chromatograph is a research tool with a well-defined function and highly specific use that does not necessitate further study of itself. It may be that a gas chromatograph may be used for a wide variety of analyses; however, this does not change its specific use for analyzing a sample. In contrast, the claimed invention is not a general tool for analyzing other samples and, at most, serves to study the function of a single gene. In this respect, the utility of a knockout mouse cannot be compared to a gas chromatograph. Therefore, the utility of the instant invention is neither specific nor substantial.

Applicant also discloses the commercial use of the claimed mice and states that commercial use and acceptance is one important indication that the utility of an invention has been recognized by one of skill in the art (page 7 of Applicant's remarks).

In response, Applicant fails to provide description or evidence of such commercial use. Applicant has not provided any evidence pertaining to what the mice are being used for and therefore, without evidence to the contrary, it is assumed that the mice are being used for the uses of record, namely in screening for drugs to treat a non-specified disease, in studying gene function and in studying gene expression (see below). As set forth above and in the previous office action, theses uses are not specific or substantial.

Applicant has stated that the mice are useful for studying expression of the ubiquitin E3 ligase gene because the mice contain a lacZ reporter gene (page 7 of Applicant's response).

In response, this too is a general utility that applies to any knockout mouse and is not specific. It is a widely used technique to generate mouse knockouts by inserting a visible reporter

gene into an endogenous gene. Just as any gene can be cloned to study gene expression, any gene can be knocked out using a lacZ construct to study function and/or expression.

Applicant has referred to the principles set forth in *In re Brana* (see pages 7, paragraph 5 of Applicant's remarks). Applicant asserts that the specification supports a use of the knockout mouse that is specific and substantial in light of the teaching of *In re Brana.*

In response, the fact pattern in *Brana* does not correlate to the fact pattern of the instant application. In *Brana*, the court addressed two separate issues, utility and enablement. The court held that the specification did, in fact, disclose a specific and substantial use for the compound, treating leukemia, and that this use was overlooked by the PTO in making the rejection under 101. The court observed that the claimed compound was similar in structure to compounds in the prior art that were useful in treating leukemia. The claimed compound behaved in a manner similar to that of the prior art in art accepted assays for anti-leukemic activity. Therefore, the specification enabled the use. The instant specification and the art of record fail to support such a patentable utility for the instant invention and therefore, the principles set forth in *In re Brana* do not apply to the instant invention.

Applicant has not addressed the rejection with respect to the findings that the sequence set forth in the specification does not encode a ubiquitin ligase E3 as taught by the specification and recited in the claims (see page 5, paragraph 2 of the previous office action). This aspect of the rejection is maintained.

In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse and cells encompassed by the claims to be credible, specific or substantial.

Claims 41-46 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition to the above enablement rejection, the following new issues of enablement arise from the newly added claims.

1) Claims 41-43,45 and 46 fail to recite a phenotype for the claimed mouse and therefore encompass any phenotype. The specification teaches only a phenotype of embryonic lethality in homozygous mice and does not teach a phenotype for heterozygous mice.

The specification has taught that mice homozygous for a disruption of the genomic locus encoding the ubiquitin ligase E3 gene that is also encoded by the cDNA set forth by SEQ ID NO:1 exhibit embryonic lethality (see page 52). The specification has not taught any other phenotype for the homozygotes as encompassed by the claims any phenotype at all for heterozygotes. In fact, the heterozygotes appear to have been indistinguishable from wildtype.

The art at the time of filing held that the phenotype of transgenic knockout mice was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that,

despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph).

Because the phenotype of a knockout mouse is unpredictable, one cannot predict or guess that the mice encompassed by the claims would exhibit any one of the infinite phenotypes broadly encompassed by the claims. The specification discloses using the claimed mice for screening for agents that affect the phenotype of the claimed mice. However, because the specification has not taught the phenotype of the mice encompassed by the claims and because the phenotype is not predictable, one of skill in the art would not know what to screen the mice for. Therefore, in light of the lack of guidance in the specification as set forth above and in light of the unpredictability of phenotype as set forth by the art, the specification fails to teach how to make and use the mice broadly encompassed by the claims.

It is noted that the newly added claims now require that the gene disruption create a null allele. The instant specification teaches only one gene disruption and does not show any evidence or characterization of the disruption or the gene product to demonstrate that the disruption disclosed is or even would likely generate a null allele. Gene disruptions can lead to hypomorphic and hypermorphic alleles. The specification does not teach how to make a null allele in a ubiquitin ligase E3 gene. Without knowing that the allele taught by the specification is a null, due the unpredictability of phenotype inherent in the art of making knockout mice, it cannot be predicted that the mice claimed, having a null allele, will exhibit the same phenotype as the mice taught in the specification. Therefore, the specification is not enabling for the person of ordinary skill in the art to make and use the claimed mouse comprising a null ubiquitin ligase E3 allele.

2) The breadth of claims 41-46 is such that they encompass chimeric mice (genetic mosaics) wherein only a portion of the cells of the mouse comprises the claimed genetic disruption. The specification fails to enable making chimeric mice such that they exhibit any phenotype, including embryonic lethality.

The phrase "transgenic mouse having a null ubiquitin ligase allele" in claim 1, line 1 is not limited to a transgenic mouse whose genome comprises a genetic disruption. The claim includes both transgenic mice and mice with a disruption in an extrachromosomal gene. The specification teaches making a chimeric mouse as an intermediate in generating a transgenic mouse whose genome comprises a disruption in a ubiquitin ligase E3 gene. However, the specification fails to outline the methods used to generate the claimed mice exhibiting any particular phenotype.

The method of making genetic mosaic mice is such that each resulting chimera is comprised of a different, unpredictable ratio of cells of various genotypes that cannot be predetermined. Therefore, the phenotype of chimeric animals is not only dependent upon the genotype of the cells (which is unpredictable for reasons set forth by the state of the art outlined above, for example see Leonard; Griffiths) but is also dependent upon the uncontrolled spatial distribution of the cells and their relative population size. Thus, the phenotype of the chimeric animals encompassed by the claims is also highly unpredictable. The specification fails to provide the guidance necessary to overcome this high level of unpredictability to generate a chimeric mouse exhibiting any specific phenotype. The specification discloses using the claimed mice for screening for agents that affect the phenotype of the claimed mice. Without a predictable phenotype, one of skill in the art would not know how to use the claimed mice

because it would require additional experimentation to determine the phenotype and to determine what to screen for. It would require undue experimentation for one of skill in the art to determine how to overcome the unpredictability associated with making chimeric animals such that the proportion and population of cells harboring a genetic alteration could be controlled in such a way as to increase the predictability of the phenotype of the resulting chimeric animal.

3) The claims are drawn to any a disruption in any ubiquitin ligase E3 gene comprising the sequence of SEQ ID NO:1. SEQ ID NO:1 is a cDNA that does not exist in the endogenous genome of a mouse. The cDNA set forth by SEQ ID NO:1 lacks intron and other gene sequences. The skilled artisan would not know how to disrupt the gene set forth by SEQ ID NO:1 because SEQ ID NO:1 does not exist in the genome of the mouse. The specification only teaches how to disrupt the endogenous genomic locus encoding the ubiquitin ligase E3 gene product that is encoded by the cDNA set forth by SEQ ID NO:1. The specification does not teach how to disrupt SEQ ID NO:1 in a mouse because that sequence does not exist in a wild-type mouse.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification and the unpredictability in the art of knockout mice, the skilled artisan would have to perform undue experimentation to determine how to make and use the claimed mice.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicant's cancellation of the rejected claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection under 35 USC 102(b) set forth on pages 8-9 of the Final Office Action mailed 01/02/04 was overcome by Applicant's amendment to claim 30 in the After Final Amendment filed 06/07/04. Applicant added the claim limitation of "...protein encoded by the gene set forth in SEQ ID NO:1". The newly added claims no longer contain this limitation but contain the limitation of "said allele comprising the sequence of SEQ ID NO:1". While this is sufficient to overcome the 102(b) rejection set forth in the Office Action mailed 01/02/04, this phrase is a grounds of rejection under 35 USC 112, first paragraph, as lacking enablement as set forth above. Applicant should keep in mind that if claims are amended to overcome the issues of enablement pertaining the limitation of "said allele comprising the sequence of SEQ ID NO:1", the art of the previous rejection may apply under 35 USC 102(b) or 103.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

Joe Woitach
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